ISSN 1063-7850, Technical Physics Letters, 2014, Vol. 40, No. 9, pp. 751–753. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © A.Yu. Elizarov, D.G. Gerasimov, 2014, published in Pis'ma v Zhurnal Tekhnicheskoi Fiziki, 2014, Vol. 40, No. 17, pp. 54–59.

A Membrane-Separator Interface for Mass-Spectrometric Analysis of Blood Plasma

A. Yu. Elizarov* and D. G. Gerasimov
Ioffe Physical Technical Institute, Russian Academy of Sciences, St. Petersburg, 194021 Russia
Kirov Military Medical Academy, St. Petersburg, 194175 Russia
**e-mail: a.elizarov@mail.ioffe.ru*
Received February 7, 2014

Abstract—We demonstrate the possibility of rapid mass-spectrometric determination of the content of anesthetic agents in blood plasma with the aid of a membrane-separator interface. The interface employs a hydrophobic selective membrane that is capable of separating various anesthetic drugs (including inhalation anesthetic sevofluran, noninhalation anesthetic thiopental, hypnotic propofol, and opioid analgesic fentanyl) from the blood plasma and introducing samples into a mass spectrometer. Analysis of the blood plasma was not accompanied by the memory effect and did not lead to membrane degradation. Results of clinical investigation of the concentration of anesthetics in the blood plasma of patients are presented.

DOI: 10.1134/S1063785014090065

The composition and concentration of drugs in the blood determine their therapeutic effect and are monitored for solving the problems of drug pharmacokinetics and pharmacodynamics. However, in the course of intravenous anesthesia with propofol ($C_{12}H_{18}O$) and fentanyl ($C_{22}H_{28}N_2O$), it is presently impossible to measure the concentration of propofol in the blood online, which hinders control of the adequacy of anesthesia.

The proposed membrane-separator interface comprises a differential pumping chamber and a mass-spectrometer chamber. The first chamber contains a poly(dimethylsiloxane) membrane with a thickness of 75 μm, which is mounted in a 10-mm-diameter hole of the interface flange with the aid of a porous titanium plate. The mass-spectrometer chamber and the differential pumping chamber are evacuated by a turbomolecular pump and its first-stage roughing pump at a rate of 60 and 20 L/s, respectively. The two chambers are separated by a 100-μm-diameter diaphragm (Pfeiffer Vacuum, Germany). A pressure drop between these chambers is distributed as 1000 mbar (pressure over the membrane)–2.0×10^{-3} mbar–1.1×10^{-5} mbar (pressure in the mass-spectrometer chamber).

The experiments were performed with a time-of-flight mass spectrometer [1] and a quadrupole mass spectrometer of the PrismaPlus type (Pfeiffer Vacuum, Germany). The separator interface design allowed the membrane to be heated to 45°C. To the present, methods were developed for measuring the absolute concentrations of a broad class of organic compounds dissolved in water, which have demonstrated the high analytical possibilities of membrane interfaces. For example, the limit of detection (LOD) achieved with quadrupole mass spectrometers is not worse than 10^{-8}–10^{-7}% (0.1–0.5 μg/L) [2, 3]. The disadvantages of membrane interfaces include a relatively large response time in comparison to that of capillary input, dependence of the membrane characteristics on the temperature, and differential selectivity with respect to various compounds.

Investigations of the separatory properties of a polymer membrane for anesthetics were performed using samples of the blood plasma. The blood samples were taken in vivo from peripheral veins during balanced inhalation anesthesia (with sevofluran level in a regime of minimum alveolar drug concentration maintained within 2–4 vol % and 0.1 mg fentanyl introduced every 20 min) and total intravenous anesthesia (with propofol or thiopental/fentanyl).

Figure 1 shows the typical mass spectrum of blood plasma taken at the initial stage of balanced inhalation anesthesia. The anesthesiologic protection of a patient was provided by propofol at a dose of 2.5 mg/kg body weight. The concentration of sevofluran in the respiratory tract of the inhalation anesthesia machine was maintained at 3 vol%, for which the concentration of compound A formed as a result of the drug interaction with soda lime amounted to 50–75 ppm.

The mass spectrum of blood plasma was obtained using electron-impact ionization at an electron energy of 70 eV. The spectrum displayed the following peaks due to parent and fragment ions of drugs (m/z, amu): sevofluran (131, 181, 199 (M^+)), sevofluran metabolite (99, 129), compound A (128, 180), propofol (163, 178), and fentanyl (146, 189). The indicated mass peaks of anesthetics correspond to the mass peaks and

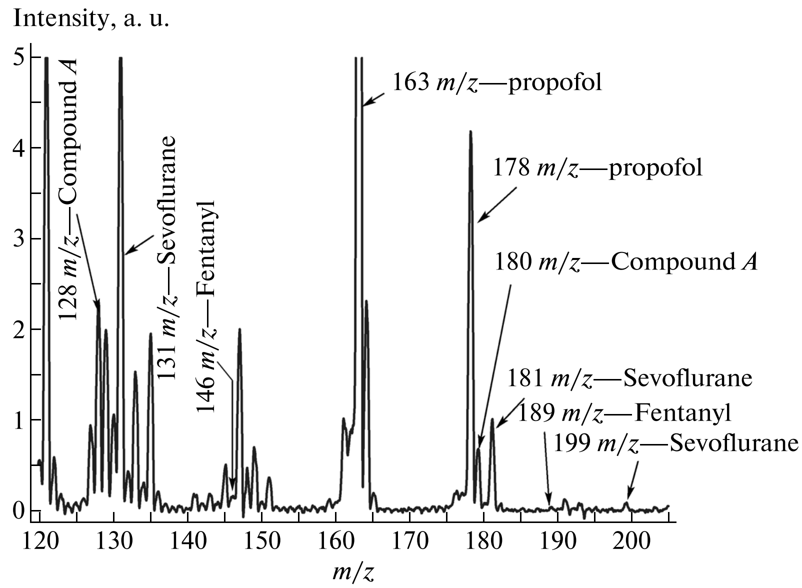

Fig. 1. Mass spectrum of blood plasma taken at the initial stage of balanced inhalation anesthesia, measured using the proposed membrane-separator interface.

their relative weights in mass spectra available in mass-spectrometry databases.

Since the membrane permeability is different for all anesthetics studied, the measurement of absolute concentrations of an anesthetic agent required calibration of its mass peak intensity with respect to an internal concentration standard of the same agent. This procedure was performed for propofol. The intravenous hypnotic propofol is almost insoluble in water, but well soluble in fats. For this reason, this agent is introduced by intravenous injections with emulsion consisting of 10% soya-bean oil, 1.2% of purified egg phospholipids (emulsifier), 2.25% glycerol, water, and sodium hydroxide (pH regulator). The emulsified form of propofol has been available in the market since 1986 and is presently the hypnotic drug of choice for inhalation or intravenous anesthesia. Figure 2 presents the mass spectrum of propofol (Fresenius-Kabi) recorded with the aid of the proposed membrane interface. The propofol emulsion was applied directly onto the interface membrane of the mass spectrometer.

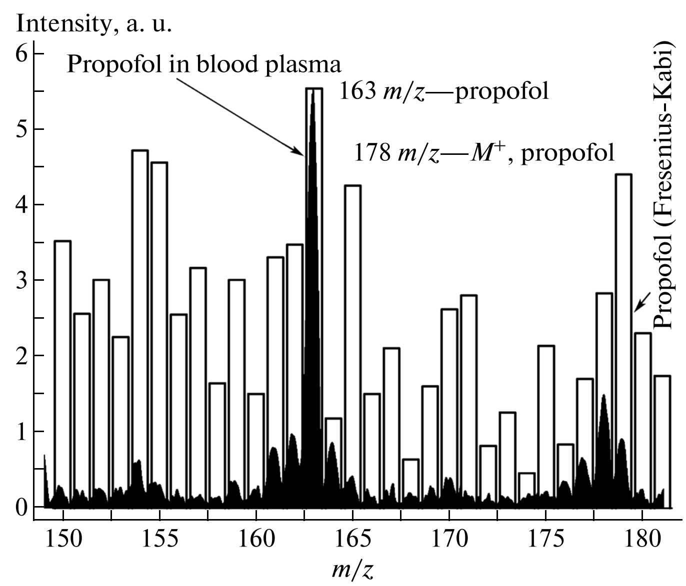

Fig. 2. Mass spectra of propofol (Fresenius-Kabi) and blood-plasma sample taken during total intravenous propofol-fentanyl anesthesia, measured using the proposed membrane-separator interface.

Figure 2 also shows the mass spectrum of a blood-plasma sample taken during total intravenous propofol-fentanyl anesthesia. Note the absence of the peaks of sevofluran, its metabolite, and compound A in this mass spectrum. Similarly, the peaks of sevofluran, its metabolite, and compound A were also not found in the mass spectra of blood samples taken during total intravenous anesthesia with thiapental and fentanyl. Thiopental was detected in the blood plasma using the mass peaks with $m/z = 157$ and 172.

During the total intravenous propofol-fentanyl anesthesia in a regime of target propofol content in the blood, the drug concentration of 3 μg/mL was set by a syringe pump (B. Brown). The blood samples were taken from peripheral veins with a 15-min interval. The internal standard was prepared in the form of a propofol solution in a parenteral (intravenous) nutrition preparation (Intralipid, Fresenius-Kabi), the composition of which corresponds to that of the propofol solvent (Fresenius-Kabi).

Figure 3 shows the EEG measured with a bispectral index (BIS) monitor (Vista, Aspect Medical Systems)

during anesthesia, from which it follows that the hypnotic-effect depth during anesthesia (5–25 min) was constant due to a stable propofol concentration in the blood. Using the membrane-separator interface and internal standard with known propofol concentration, the absolute concentration of propofol was determined in three samples of blood plasma. After every measurement, the interface was heated to 45°C and then cooled to room temperature. As a result, in a series of four measurements, the concentration of propofol in all three samples coincided to within 5%. This result demonstrates the possibility of using the proposed membrane separator interface for absolute measurements of the concentration of anesthetic drugs in blood plasma under clinical conditions.

The high solubility of propofol in lipids allows it readily penetrate through the blood–brain barrier (BBB), which explains the fast therapeutic activity of this anesthetic agent. In this study, blood was sampled from a peripheral artery and chiasma-sellar cerebral region during pituitary adenomectomy of the hypophyseal region. The results of measurements with the aid of the membrane separator interface showed that the propofol concentration in the chiasma-sellar region was 45 ± 3% lower than in a peripheral artery, which is explained by the BBB properties [4].

Upon all measurements, no traces of membrane degradation were observed. The response time of a mass spectrometer with a membrane-separator interface did not exceed 10 min, and the time of one measurement was about 1 min. The example of propofol demonstrates the possibility of using the proposed membrane-separator interface for absolute measurements of the concentration of anesthetic drugs. Owing to its simple operation and maintenance, the use of the membrane-separator interface in practical anesthesiology has good prospects for rapid determination of the concentration of anesthetic agents in the blood plasma.

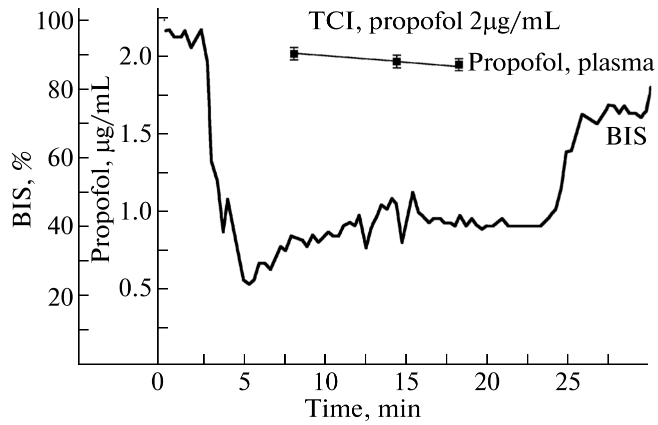

Fig. 3. Temporal variation of the propofol concentration in blood plasma and the bispectral index (BIS) during total intravenous propofol-fentanyl anesthesia.

REFERENCES

1. A. Yu. Elizarov, I. I. Faizov, A. V. Kozlovskii, and A. I. Levshankov, Instr. Exp. Tech. **56** (6), 714 (2013).
2. O. S. Viktorova, V. T. Kogan, S. A. Manninen, T. Kotiaho, R. A. Ketola, B. M. Dubenskii, S. P. Parinov, and O. V. Smirnov, J. Am. Soc. Mass. Spectrom. **15**, 823 (2004).
3. K. F. Hansen, S. Gylling, and F. R. Lauritsen, Int. J. Mass Spectrom. Ion Processes **152**, 143 (1996).
4. L. L. Rubin, K. Barbu, F. Bard, C. Cannon, D. E. Hall, H. Horner, M. Janatpour, C. Liaw, K. Manning, J. Morales, S. Porter, L. Tanner, K. Tomaselli, and T. Yednock, Ann. N. Y. Acad. Sci. **663**, 420 (1992).

Translated by P. Pozdeev